REMARKS

Applicants would like to thank the Examiner and Primary Examiner Robert Hayes for the courtesy extended in the interview of June 27, 2007 to the undersigned attorney and Applicants' attorney Joseph Williams, in which the outstanding rejections were discussed. Applicants wish to thank the Examiners for their helpful suggestions.

I. Summary of Interview of June 27, 2007 pursuant to MPEP §713.04 and 37 CFR §1.133

As noted in the Examiner's Interview Summary, mailed July 10, 2007, the rejections of claims 1-5 in view of the rejection under 35 USC §103 over the prior art Banks, Borges, and Caro were discussed.

II. Examiner's Basis for Rejection

In the Action, the Examiner maintained the rejection of claims 1-5 under 35 U.S.C. §103(a) as assertedly obvious in view of Banks et al. (*Peptides*, 17:305-11, 1996) (hereinafter "Banks") further in view of Borges (*Eur. J Pharmacology* 269:243-48, 1994) (hereinafter "Borges") and Caro et al. (*Lancet* 348:159-61,) (hereinafter "Caro"). The Examiner further rejected claim 5 under 35 U.S.C. §112, second paragraph, as assertedly indefinite. Reconsideration is requested in light of the following remarks.

III. Support for Amendment to the Claims

Support for the amendment to the claims is found throughout the specification. The amendment has been made solely to expedite prosecution, and Applicants reserve the right to pursue any cancelled subject matter in a duly filed divisional or continuation application.

The amendment includes no new matter.

IV. Patentability

A. The Rejection of Claims 1-5 Under 35 U.S.C. §103(a), Should Properly Be Withdrawn

The Examiner maintained the rejection of claims 1-5 under 35 U.S.C. §103(a) as assertedly rendered obvious over the disclosure of Banks, in view of the disclosure of Borges, further in view of the disclosure of Caro. The Examiner alleges that because Banks and Caro assertedly teach that leptin requires transport across the blood brain barrier (BBB), and Borges assertedly teaches that epinephrine increases permeability of molecules across microvascular cells in vitro, a worker of ordinary skill in the art would be motivated to combine the teachings of Banks, Caro and Borges to arrive at the present invention. Applicant respectfully disagrees.

Banks and Caro disclose that leptin is transported across the BBB by a specific, saturable transport mechanism. Borges demonstrates that epinephrine increases permeability of the BBB to the impermeable solute sodium fluorescein. In Applicant's response of 12/13/06, Applicant inadvertently (and to the Applicants' detriment) characterized Borges as disclosing that administration of epinephrine increases the permeability of microvascular endothelial cells to sodium fluorescein bound to albumin. In fact, Borges describes use of sodium fluorescein alone dissolved in buffer in the permeability assays (see abstract and p 244, col. 2), and not sodium fluorescein linked to albumin. Sodium fluorescein is a small molecule of approximately 376 Da (Abraham et al., Cell Mol Neurobiol. 22:455-62, 2002) (abstract attached hereto as Exhibit A) whereas leptin is a large protein molecule of approximately 16 kDa (see Banks et al., Brain Research, 899:209-217, 2001, ref C6 on IDS). The leptin molecule used in the examples and recited in the claims, is thus 42 times larger than the sodium fluorescein molecule used to monitor BBB permeability in Borges.

The passive transport of a small molecule across the BBB in the presence of any given permeabilizing agent cannot necessarily be taken as evidence to show that the same permeabilizing agent will induce passive transport of a much larger molecule across the BBB. More specifically, it is not proper to compare and equate transport of the two molecules of significantly different sizes, sodium fluorescein (376 Da) and leptin (16 kD), in response to administration of the non-specific BBB permeabilizing agent epinephrine. It is well-known in the art that large proteins typically do not undergo passive diffusion across the BBB, but instead are generally transported by saturable transport mechanisms (see specification page 2, lines 24-25, and page 3, lines 1-7). Because of the differences in the mechanism of transport of large and small molecules across the BBB and the difficulty in inducing passive diffusion of large molecules across the BBB, one of ordinary skill would not be motivated by Borges to use epinephrine to attempt to enhance leptin uptake into the brain, much less have any expectation that using such a method would be successful.

Even if one were to incorrectly conclude that the combined prior art would have provided the worker of ordinary skill with a reasonable expectation of success, results from use of the claimed method in the instant application would have been wholly unexpected. Example 2 of the specification (beginning on page 19) teaches that administration of exogenous leptin in conjunction with 2 nM epinephrine increases leptin uptake across the BBB by 17%, administration of 40 nM epinephrine resulted in approximately a 155% increase in leptin uptake, and administration of 100 nM epinephrine resulted in approximately a 200% increase in leptin uptake. In contrast, Borges shows that administration of 100 nM epinephrine increased transport of sodium fluorescein across the BBB only by approximately 34% (Borges, page 245, col 2). More pointedly, at the same concentration of 100 nM epinephrine, passive diffusion of the small molecule increased by 34% while transport of the much larger leptin molecule increased by

nearly 200%, an approximately 6 times greater increase in transport which the art does not predict.

Because Borges teaches that epinephrine is a non-specific permeabilizer of the BBB to small molecules such as sodium fluorescein, and it is commonly known in the art that large proteins do not generally diffuse across the BBB, even if the BBB is permeabilized (see Nanoka et al., Brain Res. 1016:58-65, 2004, submitted in Applicants response of 12/13/06 and Banks et al., ref C6), there would be no expectation of success at enhancing transport of the large protein leptin by administering epinephrine, much less enhancing transport to the unexpected degree shown in the instant application. Accordingly, the rejection of claims 1-5 under 35 U.S.C. §103(a) should be withdrawn.

B. The Rejection of Claim 5 Under 35 U.S.C. §112, Second Paragraph, Should Properly Be Withdrawn

The Examiner rejected claim 5 under 35 USC §112, second paragraph, asserting that the claim recited an improper antecedent basis. Cancellation of the claim obviates the Examiner's rejection.

V. Conclusion

Applicants submit that the application is now in condition for allowance and respectfully request notice of the same.

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Respectfully submitted,

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